Infantile Enuresis: Current State-of-the-Art Therapy and Future Trends

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Enuresis nocturna is a widespread problem among children, with up to 25% of all children possibly suffering from this condition. Several therapeutic modalities are currently available. This article reviews current state-of-the-art therapies, highlights current literature, and provides an update on recent developments within the field of enuresis nocturna.
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Enuresis nocturna is the involuntary loss of urine during the night in the absence of organic disease. It is a very common pediatric issue, of which the prevalence of children who may suffer from this condition is estimated at 3.8% to 25%. In contrast to the relatively high percentage seen among children, only 1% to 2% of adults suffer from this disorder. This is a result of the increasing number of children who spontaneously achieve nighttime bladder control. Current data suggest an annual healing rate of 15%.[1]

Monosymptomatic enuresis (ME) and nonmonosymptomatic enuresis (NME) have to be differentiated before any kind of therapy protocol is initiated. The most important criterion of ME is the absence of bladder dysfunction, whereas NME is defined by the concomitance of bladder dysfunction such as urge incontinence or dysfunctional voiding. It has been shown that true ME is found in less than one-half of cases of enuretic children. The exact etiology of nocturnal enuresis is multifactorial; however, ME has a significant correlation with arousal problems, overnight polyuria, and overactive detrusor activity.

Enuretic children often suffer from low self-esteem due to tension with their parents caused by the involuntary loss of urine, social marginalization, and frequent therapy-refractory symptoms. Families with enuretic children should be counseled from the beginning with general lifestyle advice. Active therapy modalities should not be started before age 6 years.[2]

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General Lifestyle Advice

The affected families should be adequately informed about the pathogenesis of enuresis nocturna. Individual goals for each child should be established, and these aims should be realistic and attainable for the enuretic child. The best approach is to encourage families to keep a micturition diary, in which dry and wet nights are noted thoroughly. This will help parents to perceive improvements in their child's condition and alleviate unnecessary tension and pressure within the family. Another basic step would be the recommendation to better distribute daily fluid intake as well as the adherence to regular micturition. Furthermore, it should be made clear that any signs of constipation should be treated (eg, stool softener, diet changes, etc) to prevent involuntary nighttime urine loss. From the psychologic point of view, it must be stressed that enuresis nocturna is neither the fault of the child nor the parents in their education of the child.[2]

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Therapy Modalities Using an Alarm

Various types of gadgets are being used to combat enuresis nocturna. The current literature indicates that, in two-thirds of cases, alarm therapy leads to a positive outcome.[3] However, the effect of this therapy corresponds to the cooperation and motivation of the parents. It is their duty to ensure that the enuretic child goes to the toilet when the alarm is triggered. An evaluation of the therapy outcome should be reviewed after a period of 2 to 3 months. If no sign of improvement is seen within that time frame, the therapy should be adjusted.[4]

Desmopressin

Besides alarm therapy, the antidiuretic hormone desmopressin is perceived as first-line therapy in enuretic children. Recent studies show that almost one-third of children treated with desmopressin develop full bladder control at night. Another 40% show significant improvement/decrease in the quantity of wet nights.[5] The effect of desmopressin is best seen in enuretic children with nightly polyuria (urine production > 130% of the expected bladder capacity).

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Overall, desmopressin is a safe drug with mild reported side effects. The only bothersome problem is the combination of desmopressin and increased fluid intake. In this case, water intoxication has been documented, which has resulted in clinically relevant hyponatremia and consecutive convulsions. Recent reports suggest that the risk of this complication is higher when nasal sprays are used.[6] A general recommendation regarding fluid intake for families using desmopressin is to limit the evening fluid intake to ≤ 200 mL, and then no fluids until the morning hours. Desmopressin tablets should be taken at least 1 hour before going to bed because the maximum antidiuretic effect is attained after 1 to 2 hours. If this medication helps the child to deal with the involuntary nighttime urine loss, then a decision must be made whether desmopressin is used on a daily basis or if it is used on particular occasions. Families electing the daily use option must be informed that drug-free weekends should be held every so often to evaluate the indication of the medication.

If no real indication persists, the use of this antidiuretic medication should be discontinued. Recent data show that a gradual reduction of intake correlates with a better outcome than an abrupt ending of the therapy. Marschall-Kehrel and colleagues[5] analyzed the effect of a gradual reduction of the frequency of desmopressin intake. The group of children with abrupt ending of desmopressin therapy (n = 173) showed a decrease in wet nights from 21 to 6. In contrast,

the group with gradual frequency reduction (n = 314) showed a diminishment from 21 wet nights to only 2 per month. The 1-month follow-up after therapy cessation showed that fewer than two wet nights per month were reported in 80% of cases in the group with gradual reduction of therapy frequency, however, this effect could only be demonstrated in 57% of the group with abrupt therapy ending ($P < 0.01$). These results were statistically significant and showed quite clearly how important it is not to stop desmopressin therapy without any dosing scheme or frequency reduction.

Several studies have shown the great potential of combination alarm therapy gadgets with desmopressin.[7-9] Leebeck-Groenevegen and associates[7] provided evidence that a combination of both therapies led to a significant reduction of wet nights after 3 weeks compared with the results of alarm monotherapy in combination with placebo. Vogt and colleagues[9] investigated the question of whether a combination of alarm therapy and desmopressin is more effective in the treatment of enuretic children. Group A consisted of 16 children who received desmopressin from the beginning of the study, and after 3 months, also received alarm therapy for an additional 3 months. Group B, however, received the same treatment vice versa. The study group concluded their results after 6 months of treatment. In Group A, 11 of 16 children were reported to be continent (< 3 wet nights per month); in Group B, 11 of 14 were reported to be continent. The authors concluded that there was no difference with regard to which type of therapy began first.

Anticholinergics

Children suffering from idiopathic overactive bladder (OAB) will receive general lifestyle advice as first-line therapy. This so-called urotherapy is a nonoperative, nonpharmacological therapy modality that focuses on the application of drinking and micturition protocols and on the therapeutic effect of modifications to daily habits regarding micturition and fluid intake. If this conventional method fails, anticholinergic substances are often used.

Currently, three different anticholinergics are available on the market—oxybutynin, tolterodine, and propiverine. None of these substances should currently be used as first-line therapy for enuresis nocturna treatment. The use of anticholinergics should be thoroughly considered. A clear indication is only given if the standard therapy regimen does not bring any benefit. Data show that almost 40% of the children who do not experience any symptom improvement with conventional methods will benefit from anticholinergics; however, desmopressin is often needed as a combination therapy.[10] The maximum antidiuretic effect should be seen approximately 2 months after initiating therapy. The most common side effect is constipation, and the greatest risk comes from residual urine that can cause recurrent urinary tract infections.

Hoebeke and associates[11] focused on the effects of solifenacin as a therapy modality for OAB. Solifenacin belongs to the same group of antimuscarinic substances as darifenacin and fesoterodine. Investigations on adults[12] have already taken place; however, there are still no data available on children. In Hoebeke's study, 84 boys and 54 girls were treated with solifenacin. The authors reported only 9 of 138 cases experiencing side effects (6.5%). The median urine volume per micturition could be elevated significantly from 203 mL to 253.5 mL (+25%) under therapy conditions. A total of 84 children (85%) benefited from the therapy: 45 children became totally dry and 39 children had a partial response from therapy. From these 39 children, 17 became dry during the day, 1 was continent at night only, and 21 had a reduction of > 50% of enuresis episodes. These results showed the promising potential of solifenacin.

Tricyclic Antidepressants

The tricyclic antidepressant imipramine has been tested extensively as a potential medication for enuresis nocturna. Placebo-controlled, randomized studies have clearly shown its efficacy; almost 50% of treated children experienced some kind of benefit from therapy.[13] But due to its side effects as well as the security concerns, imipramine is still considered a third-line therapy modality. The biggest concern when using this substance is its potential cardiotoxicity.

Lundmark and Nevéus analyzed the effects of the noncardiotoxic antidepressant reboxetine.[14] A total of 32 of the 61 children in this study benefited from reboxetine (51%); 21 of them after combination with desmopressin. These results clearly indicate that reboxetine is a valid alternative option for therapy-resistant enuresis. More randomized, prospective trials are necessary to make exact conclusions. Reboxetine is still not authorized for pediatric use; however, several studies are currently ongoing and results are expected in the near future. The initial idea of a potential antienuretic drug was born during neuropsychiatric studies, when an antienuretic effect was unexpectedly discovered among children using this medication.

Recent Developments

Although enuresis nocturna is a common pediatric problem, its exact pathogenesis is still not completely understood. A group of Australian authors tried to identify risk factors

for nighttime urine loss. A total of 2856 parents of enuretic children cooperated with this study (mean age of the children, 7.3 ± 1.3 years). The prevalence of enuresis was 18.2% among those children: 12.5% were considered to have mild symptoms, 2.5% had moderate symptoms, and 3.6% were reported to have severe enuretic problems. Multivariate analyses showed that urinary incontinence during the day (odds ratio [OR] 4.8%; 95% confidence interval [CI], 2.9-7.9), encopresis (OR 2.7; 95% CI, 1.6-4.4), bladder dysfunction (OR 3.6; 95% CI, 2.4-5.3), and male sex (OR 2.0; 95% CI, 1.3-3.1) were significantly associated with severe nightly urinary incontinence. Emotional stress (OR 2.3; 95% CI, 1.2-4.2) and social fears (OR 2.4; 95% CI, 1.2-4.5), however, were associated with mild enuresis nocturna.[15]

Another very interesting finding comes from Kruse and associates.[16] These authors demonstrated that children with enuresis nocturna caused by polyuria have a higher mean arterial pressure at night than normal children.

Giggle incontinence (GI) or enuresis risoria is a small subset of urinary incontinence. It is provoked by laughter with no forewarning.[17] GI is very seldom encountered and is predominantly seen among girls and women. The pathogenesis of this incontinence subtype is still not truly understood, although several studies suggest a functional relationship to cataplexy. Berry and colleagues[17] analyzed the therapeutic effect of methylphenidate for GI. The retrospective design of the study limits its significance; however, promising data were revealed. A total of 15 of the 20 children with GI in this study received methylphenidate as a therapy regimen; 12 (80%) reported a total cessation of GI after the methylphenidate intake.[17] One reported problem with this substance is that parents do not fully accept methylphenidate because its primary use is for children with attention deficit hyperactivity disorder.

Pelvic floor muscle exercises are fully established as a valid therapy option in adults dealing with urinary incontinence. Hence, the question arises if a combination of pelvic floor muscle exercises and current first-line therapy for enuresis nocturna leads to a better outcome. Van Kampen and colleagues analyzed the potential effect of pelvic floor muscle exercises in combination with full-spectrum therapy for nocturnal enuresis.[18] Full-spectrum therapy is defined as the combination of alarm therapy, reward, and timed voiding and drinking. A total of 63 children were included in this study: 32 belonged to the group receiving combination therapy and 31 were randomized into the conventional therapy group. The authors concluded that there was no significant difference between these therapy modalities. After 6 months, 89% of all children were continent. Approximately 33.3% and 37.9% of the experimental and conventional groups, respectively, suffered from an enuresis recurrence.

In conclusion, it is suggested that therapy-resistant children may benefit from regular new attempts with conventional first-line therapy methods. The fact that a therapy did not work previously does not mean that it will not work going forward. Data indicate that different combinations may enhance the therapeutic effects of the standard therapy regimen. ■

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Main Points

- Data indicate that different combinations may enhance the therapeutic effects of the standard therapy regimen for enuresis nocturna. Families should be counseled on lifestyle advice, and realistic goals for the child should be established. Basic steps include better distribution of daily fluid intake as well as the adherence to regular micturition.
- The antidiuretic desmopressin is perceived as first-line therapy in enuretic children. Studies show that almost one-third of children treated develop full bladder control at night, and another 40% show significant decrease in the quantity of wet nights. In addition, several studies have demonstrated great potential of combination alarm therapy with desmopressin.
- The anticholinergic substances—oxybutynin, tolterodine, and propiverine—are often used if standard regimens fail. None should be used as first-line therapy for treatment, and their use should be thoroughly considered. Data show that almost 40% of children may benefit from anticholinergics, although desmopressin is often needed as a combination therapy.
- Studies indicate that almost 50% of children treated with the tricyclic antidepressant imipramine may benefit from this therapy, although due to its side effects and potential cardiotoxicity, it is still considered a third-line therapy modality.
- Therapy-resistant children may benefit from regular new attempts with conventional first-line therapy methods. Because a therapy did not work previously does not mean that it will not work going forward. Data indicate that different combinations may enhance the therapeutic effects of the standard therapy regimen.

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